REMARKS

Claims 1-22 were pending in this application. Claims 1and 8 have been amended.

Support for the amendment of claims 1 and 8 can be found throughout the specification, including page 2, lines 1-32; and page 17, line 1 to page 18, line 10.

Applicants believe no new matter is introduced by the foregoing amendments. After entry of this amendment, **claims 1-22 are pending in this application**. Reconsideration of the pending claims is requested.

The amendment to claims 1 and 8 was addressed at page 8 of the final Office action. The specification at page 2, lines 13-15, also makes it clear the method can be used to treat someone who is otherwise well and not depressed as a result of another medical problem. Thus, Applicants submit that the claim amendment does not raise new issues requiring an additional search. This response is submitted within two months of the mailing date of the final Office action. Applicants believe that the application will be in condition for allowance following entry of this amendment. In the unlikely event that an Advisory Action is issued and that it is not mailed until after the end of the three month shortened statutory period, then it is the Applicant's understanding that the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee will be calculated from the mailing date of the Office action.

Rejections Under 35 U.S.C. § 103

Claims 1-15 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Murray et al., in view of Binder et al., and further in view of Caruthers et al. Applicants respectfully disagree with this rejection as applied to the claims as amended.

Murray et al. teach the treatment of spasmodic dysphonia, a neuromotor disorder that affects the voice. Murray et al. describe that treatment of subjects with botulinum toxin by injecting the toxin in the thyroidarytenoid muscle, a muscle in the neck. Injection of botulinum toxin into the neck of patients with spasmodic dysphonia resulted in reduction of voice breaks. Murray et al. conclude that decreases in voice breaks due to the injection of botulinum toxin in the neck could result in a decrease in depression.

Thus, Murray et al. teach that the decrease in voice breaks due to injection of botulinum toxin into the neck muscles might reduce situational depression solely by affecting voice breaks. Murray et al. do not teach, nor render obvious, the use of botulinum toxin to treat primary depression or primary anxiety and depression (in the absence spasmodic dysphonia or an underlying physical condition that causes the mood disorder). Moreover, Murray et al. do not teach, nor render obvious the treatment of primary major depression, which is a distinct psychiatric disorder (see, for example, the specification at page 2, lines 13-15).

Binder teaches the reduction of headache pain by injecting botulinum toxin. Binder et al. suggest the extra-muscular injection of botulinum toxin. Binder et al. do not discuss the treatment of primary depression.

Caruthers et al. teach the cosmetic use of botulinum toxin to paralyze the depressor anguli oris muscle to alleviate downturn of a subject's mouth. Caruthers et al. do not suggest the use of a toxin to treat any emotional disorder, let alone a depression.

As discussed in the response submitted on December 26, 2006, there is nothing in the teachings of Murray et al, on the treatment of spasmodic dysphonia that either explicitly or implicitly suggests combination with the teachings of Binder et al., on the treatment of headaches, or with the teachings of Caruthers et al. on cosmetic uses for botulinum toxin for the treatment of a down turned mouth. Even if one were to make this *impermissible* combination, one would merely arrive at treating spasmodic dysphonia or headaches (perhaps secondary to spasmodic dysphonia) by injecting botulinum toxin into a facial muscle (which likely would not work for the treatment of underlying spasmodic dysphonia).

It is possible that the alleviation of the headaches or the spasmodic dysphonia might alleviate minor depression secondary to these conditions. There is nothing in any of Murray et al., Binder et al., or Caruthers et al., even in combination, that would suggest, or render obvious, the selection of a patient with primary depression, the treatment of primary depression (claim 1 and claims that depend therefrom), primary intermittent anxiety and depression (claim 8 and claims that depend therefrom) or primary major depression (claim 22) with botulinum toxin. The references only suggest selection of subjects who have dysphonia or headaches. Although some of these subjects may incidentally be depressed that does not disclose the claimed step of selecting a subject (as claimed) because the subject is depressed. In the absence of a disclosure of this step, the *prima facie* case of obviousness has not been established.

The Office action alleges that Murray et al. teach the treatment of "major depression" as the subjects were "highly depressed patients" based on a score on the self-rating of depression scale (SDS) of 50 to 53. However, a patient with an SDS score of 50 to 53 is not a patient that would be clinically diagnosed with major depression. Attached as Exhibit A is a printout of the SDS test, and a scale showing the scoring guidelines on the SDS. A score of 50-59 is considered to indicate the presence of "minimal to mild" depression. A score of 70 and over is considered "sever or extreme depression." A "major depression" as characterized by the by the DSM-IV (see the description provide in the specification at page 7-32) is a severe condition, wherein the individual is "unable to function in everyday life," "have feelings of extreme hopelessness," "have diagnostic criteria associated with DSM-IV 296.2 and 296.3," and are associated with a severe risk of suicide." Someone with major depression simply would not be ranked with a score of 50-53 on the SDS, but likely would be ranked with a score of 70 and over. Thus, Murray et al., even in combination with Binder et al. and Caruthers et al., does not suggest or render obvious the treatment (or alleviation) of primary major depression.

Moreover, the Applicants have submitted evidence of the unexpectedly superior results obtained using the claimed methods. The documentation of the unexpected superior results obtained using the claimed methods overcome any *prima facie* case of obviousness that could be made over the impermissible combination of Murray et al, Binder and Caruthers et al. Specifically, the prior art does not contain any suggestion that depression can be treated without firs treating an underlying disorder, such as dysphonia. It is unexpected that primary depression responds to injection of a neurotoxin that decreases ability of the subject to frown. None of the cited references, alone or in combination, suggests a method of treating depression in a subject by selecting a subject with primary depression. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 1-15 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Jahanshahi et al., in view of Binder and Caruthers et al.

Jahanshahi et al. teach that depression in torticollis patients is secondary to the postural abnormality of the head (see page 229, first column), and constitutes "a reaction to the disorder." Botulinium toxin was injected into the superficial neck muscles (not facial muscles) of subjects to treat torticollis (see page 229, second column). The aim of the results presented by Jahanshahi

et al. was to assess "improvement of torticollis with botulinum toxin injection accompanied by improvement of depression, reduction of disability, and improvement of the negative body concept and low self esteem" (see page 229, second column). Jahanshahi et al. report that the injection of botulinum toxin into the superficial neck muscles results in straightening of the head and relief from neck pain, and *reduction of depression and disability associated with head position and pain* (page 231, first column). Jahanshahi et al. conclude that the improvement of depression was a "non-specific result" and that it "provides support for the reactive nature of depression and disability in a proportion of torticollis patients" (page 231, second column). Thus, Jahanshahi et al. *teach away* from the use of botulinum toxin to treat primary depression, with underlying torticollis.

Binder et al. and Caruthers et al. are discussed above. As discussed in the response submitted on December 26, 2006, there is nothing in the teachings of Jahanshahi et al, on the treatment of torticollis that would suggest combination with the teachings of Binder et al., on the treatment of headaches, or with the teachings of Caruthers et al. on cosmetic uses for botulinum toxin. Even if one were to make this *impermissible* combination, one would merely arrive at treating torticollis or headaches (perhaps secondary to torticollis) by injecting botulinum toxin into a facial muscle. This method likely would be an inoperable for the treatment of torticollis. There is nothing in any of Jahanshahi et al., Binder et al., or Caruthers et al., even in combination, that would suggest, or render obvious, the selection of a patient with primary depression, the treatment of primary depression (claim 1 and claims that depend therefrom), primary intermittent anxiety and depression (claim 8 and claims that depend therefrom) or primary major depression (claim 22) with botulinum toxin.

Moreover, the Applicants have submitted evidence of the unexpectedly superior results obtained using the claimed methods. The documentation of the unexpected superior results obtained using the claimed methods overcome any *prima facie* case of obviousness that could be made over the impermissible combination of Murray et al, Binder and Caruthers et al. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 16-21 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Jahanshahi et al., Binder and Caruthers et al. in view of Wagstaff et al. (abstract only). Applicants respectfully disagree with this rejection.

Jahanshahi et al., Binder and Caruthers et al. are discussed above. Wagstaff et al. teach that paroxetine (a selective serotonin reuptake inhibitor, SSRI) is effective at treating depression, obsessive-compulsive disorder, and panic disorder. There is nothing in Wagstaff et al., absent the teachings of the subject application that would suggest combination with Jahanshahi et al. (on the treatment of torticollis), Binder et al. (on the treatment of headache) or Caruthers et al. (on cosmetic uses for botulinum toxin). Moreover, even if one were to make this *impermissible* combination, one would merely arrive at treating a subject having torticollis (perhaps with minor depression secondary to torticollis) or headaches (perhaps secondary to torticollis) by injecting botulinum toxin into a facial muscle, and also using a SSRI. This method likely would be inoperable for the treatment of torticollis.

There is nothing in any of Jahanshahi et al., Binder et al., or Caruthers et al., even in combination, that would suggest, or render obvious, the selection of a patient with primary depression, the treatment of primary depression (claim 1 and claims that depend therefrom), primary intermittent anxiety and depression (claim 8 and claims that depend therefrom) or primary major depression (claim 22) with botulinum toxin. Thus, there is nothing to suggest the treatment of a subject with primary depression with both botulinum toxin and an SSRI.

Moreover, the Applicants have submitted evidence of the unexpectedly superior results obtained using the claimed methods, specifically documenting the superior results obtained with the injection of botulinum toxin and the use of additional treatment modalities, even when the use of PAXIL and ZOLOFT have failed in the patient. The documentation of the unexpected superior results obtained using the claimed methods overcome any *prima facie* case of obviousness that could be made over the impermissible combination of Murray et al, Binder and Caruthers et al. Reconsideration and withdrawal of the rejection are respectfully requested.

Conclusion

Applicants believe the present application is ready for allowance, which action is requested. The prior response included a written request for an interview under MPEP §713.01, (which indicates that an interview can be arranged in advance by a written request). However, the Examiner did not contact the undersigned for an interview prior to the issuance of the final Office action. If any matters remain to be discussed before a Notice of Allowance is issued, the

Examiner is respectfully requested to contact the undersigned for a telephone interview at the telephone number listed below.

Respectfully submitted,

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By _____
Susan Alpert Siegel, Ph.D.
Registration No. 43,121

Facing depression or even just acknowledging its presence can be difficult. This test is adapted from the test used for the National Depression Day Screening which is conducted every October, nationwide. For a confidential email, online chat or phone session with a therapist, visit **www.eTherapistsOnline.com**

Read each sentence carefully. For each statement, check the bubble in the column that best corresponds to how often you have felt that way during the past two weeks. Simply click on the appropriate button then, when you have answered *all* of the questions, click the Total button. You can print this form and manually apply the values shown to the right for each answer. Your privacy is respected here. Your results are not reported in any fashion. They are for your use and the use of your therapist.	1 None or little of the time	2 Some of the time	3 Good part of the time	4 Most or all of the time
1. I feel downhearted, blue, and sad.	○1	○2	○3	○4
2. Morning is when I feel the best.	○4	○3	○2	○1
3. I have crying spells or feel like it.	○1	○2	○3	○4
4. I have trouble sleeping through the night.	○1	○2	○3	○4
5. I eat as much as I used to. (If you are on a diet, answer as if you were not.)	○4	○3	○2	○1
6. I enjoy looking at, talking to, and being with attractive women/men.	○4	○3	○2	○1
7. I notice that I am losing weight. (If you are on a diet, answer as if you were not.)	○1	○2	○3	○4
8. I have trouble with constipation.	○1	○2	○3	○4
9. My heart beats faster than usual.	○1	○2	○3	○4
10. I get tired for no reason.	○1	○2	○3	○4
11. My mind is as clear as it used to be.	○4	○3	○2	○1
12. I find it easy to do the things I used to do.	○4	○3	○2	○1
13. I am restless and can't keep still.	○1	○2	○3	○4
14. I feel hopeful about the future.	○4	○3	○2	○1
15. I am more irritable than usual.	○1	○2	○3	○4
16. I find it easy to make decisions.	○4	○3	○2	○1
17. I feel that I am useful and needed.	○4	○3	○2	○1
18. My life is pretty full.	○4	○3	○2	○1
19. I feel that others would be better off if I were dead.	○1	○2	○3	○4
20. I still enjoy the things I used to do.	○4	○3	○2	○1

Please also answer Yes or No to the following three questions:		Yes	No	
A. Have you ever had at least a four-day period of sustained, excessively elevated mood, with rapid thinking, many new ideas, heightened interest in sex, and loss of sleep?		○	◉	
B. Have you ever had at least a four-day period of sustained, excessivly irritable mood, with anger, arguments, or breaking things, that led to difficulties with others?		○	◉	

C. Has any close blood relative ever had depression, manic-depression, alcohol abuse, or been psychiatrically hospitalized?		○	◉
	Total	Raw Total:	0

STEP 2: Note your SDS Index score from the number next to your raw total in the following table:

Conversion of Raw Scores to the SDS Index

Raw Score	SDS Index	Raw Score	SDS Index	Raw Score	SDS Index	Raw Score	SDS Index	Raw Score	SDS Index
20	25	32	40	44	55	56	70	68	85
21	26	33	41	45	56	57	71	69	86
22	28	34	43	46	58	58	73	70	88
23	29	35	44	47	59	59	74	71	89
24	30	36	45	48	60	60	75	72	90
25	31	37	46	49	61	61	76	73	91
26	33	38	48	50	63	62	78	74	92
27	34	39	49	51	64	63	79	75	94
28	35	40	50	52	65	64	80	76	95
29	36	41	51	53	66	65	81	77	96
30	38	42	53	54	68	66	83	78	98
31	39	43	54	55	69	67	84	79	99
								80	100

STEP 3: What Your Scores Mean

SDS Index — Equivalent Clinical Global Impression

Below-50 ... Within normal range, no psychopathology.

50 - 59 ... Presence of minimal to mild depression.

60 - 69 ... Presence of moderate to marked depression.

70 & over ... Presence of severe to extreme depression.

For a complimenatry initial consultation, print the results of your test and bring it with you.

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